

REMARKS

Claim 20 has been amended to depend from claim 18 and to include the phrase "pharmaceutical carrier." Basis for this amendment appears in the specification, for example, on page 20, lines 24-26. Claim 25 has been deleted. Claims 18-20, 22, 23, and 29 are pending in the application. Attached hereto is a copy of Claim Amendments with Markings to Show Changes Made. For convenience, the pending claims are set forth in Appendix A. A supplemental Information Disclosure Statement and PTO Form 1449 is submitted herewith, listing WO 98/13493. Applicants note that SEQ ID NO:3 of WO98/13493 corresponds to SDF-5.

During preparation of the response to the outstanding utility rejection, it was determined that the inventorship required correction. Applicants have prepared the documentation required to add Kimberly Gillis, Maximillian Follettie and Gary Hattersley as inventors and as soon as this documentation is executed, it will be submitted.

Double Patenting

Claims 18-20, 22, 23, 25, and 29 are provisionally rejected under the judicially-created doctrine of double patenting over claims 18-20, 22, 23 and 25 of copending USSN 08/848,439. Applicants note the Examiner's intention to hold the double patenting rejection in abeyance until such time as either USSN 08/848439 or the instant application is found allowable.

Rejections Under 35 USC §101

Claims 1-8 are rejected under 35 USC §101 as allegedly not supported by a substantial utility, a well-established utility, or a credible utility. At the outset, Applicants point out that claims 1-8 are not in the Application. Based on the content of the

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rejections, Applicants have assumed this is a typographical error and have treated the rejection as pertaining to all pending claims.

Applicants submit that the claimed invention is supported by a substantial, well-established utility, and credible utility. Support for the utility of SDF-5 in the formation and/or maintenance of chondrocytes and/or cartilaginous tissue is found throughout the specification. For example, this utility is based on the localization of the expression of SDF-5 and the *in vitro* activity set forth in Example 7. As set forth in Example 7, *in situ* hybridization to localize SDF-5 mRNA in mouse embryos demonstrated that SDF-5 is expressed in the developing joints of the appendicular skeleton and in some tendons and ligaments. Expression was not detected in bones of the axial or appendicular skeleton or in muscle (page 52, lines 35-53). Based on these results, it was considered likely that cartilage formation would be regulated by SDF-5. Therefore, assays were carried out as set forth in Example 7. MLB13MYC-clone 14 cells were treated with BMP-2 resulting in the expression of hypertrophic cartilage and bone marker genes, together with low cartilaginous markers. In untreated cells or cells treated with SDF-5, there was no detectable expression of genes characteristic of a bone or cartilage phenotype. However, when cells were treated with a combination of SDF-5 and BMP-2, both bone and hypertrophic cartilage markers were significantly decreased or absent, while markers for cartilage were increased compared with BMP-2 (page 53, lines 10-26). This decrease in bone and hypertrophic cartilage markers and the concomitant enhancement of cartilage phenotype with the SDF-5/ BMP-2 combination indicates that SDF-5 blocks the transition of differentiating chondrocytes into osteoblasts and at the

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same time shifts the cells to become chondrocytes. This implies that SDF-5 is blocking Wnt activity and that both BMP-2 and Wnt(s) are required for osteoblast differentiation.

To further support the utility of SDF-5 in the maintenance and/or formation of chondrocyte and/or cartilaginous tissue, Applicants submit herewith in Attachment A further evidence that SDF-5 (SFRP-2) is capable of blocking Wnt activity in osteoblasts. The Luciferase Assay set forth in Attachment A measures Wnt activity and utilizes mature osteoblasts. The assay results demonstrate that SDF-5 (SFRP-2 in the graphs) suppressed TCF- luciferase activity in the hOB cells. These observations demonstrate SDF-5 is capable of blocking Wnt activity in osteoblasts.

This data is indicative of the ability of human SDF-5 protein to regulate the binding of Wnt proteins to protein receptors and thereby the ability to enhance and/or inhibit the formation, growth, proliferation, differentiation, and/or maintenance of chondrocytes and/or cartilage tissue, which, as the Examiner points out, is suggested in the specification (p. 5, lines 7-17). These proteins may be useful in the treatment of cartilage disorders such as osteoarthritis, rheumatoid arthritis, and articular cartilage defects (p. 11, lines 24-31). Thus, contrary to the Examiner's contention, the specification and record does teach a substantial, credible, or well-established utility for the claimed polypeptide products.

As is apparent from the discussion of the assays set forth above, the asserted utility of the SDF-5 polypeptide is based on more than homology to the Wnt binding domain of frizzled/frazzled family of proteins (p. 4, lines 5-15) and homology to murine SDF-5 as the Examiner contends. Despite the Examiner's contention that, at the time the invention was made, there was not a single Wnt family protein and that the Wnt

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family of proteins consists of more than a dozen structurally-related molecules involved, as extracellular signaling molecules, in cellular proliferation, migration, differentiation, and tissue morphogenesis (Finch et al. PNAS 1997 94:6770-6775), Applicants have demonstrated the utility of SDF-5 in the formation and/or maintenance of chondrocyte or cartilaginous tissue. Despite the Examiner's contention that the Frizzled family is a large family of putative transmembrane receptors, 19 of which have been identified and likely to play multiple roles in vertebrate development and/or physiology (Wang et al JBC 271: 4468-4476); and that the expression of frizzled family members in many different tissues and during embryonic development suggests that they are involved in a wide variety of developmental and/or homeostatic processes, Applicants' disclosure provides a utility for SDF-5 in chondrocyte or cartilaginous tissue maintenance and/or formation as described above.

Applicants respectfully disagree with the Examiner's contention that the specification need teach which of the more than a dozen Wnt proteins SEQ ID NO:2/3 would be capable of binding or which receptor binding interactions SDF-5 would be capable of regulating. The specification teaches that the encoded protein of SEQ ID NO:2/3 may be capable of binding the Wnt proteins and thus capable of regulating the binding interaction of Wnt gene products to receptor proteins. As described above, Applicants have established that SDF-5 is, in fact, capable of antagonizing Wnt signaling.

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Rejections Under 35 USC §112

Claim 20 is rejected for allegedly failing to provide sufficient guidance to enable one skilled in the art to use a composition comprising a therapeutic amount of at least one human SDF-5 polypeptide. Previous amendments to claim 20, to depend from claim 18 and to include the phrase "in a pharmaceutical carrier," were not entered by the Examiner. These amendments are, therefore, presented once again herein, thereby overcoming the rejection.

The Examiner contends that although claim 20 is now drawn to chondrocyte and/or cartilaginous tissue formation and/or maintenance, the specification is not enabling for the *in vivo* treatment of any disease or condition. For the reasons set forth above, Applicants contend that the specification is enabling for the formation and/or maintenance of chondrocyte and/or cartilaginous tissue and thus the *in vivo* treatment of related diseases or conditions.

Claims 18-20, 22, 23, 25, and 29 are rejected under U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention. The Examiner's contentions with respect to this rejection parallel those set forth above under the §101 rejections. For the reasons discussed above, Applicants submit that claims 18-20, 22, 23, and 29 as amended are directed to subject matter described in the specification enabling to one skilled in the art and therefore his rejection has been overcome.

The Examiner indicates that if Applicant were able to overcome the rejections under 35 USC §101 and 35 USC §112 first paragraph above, Claim 25 would still be

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rejected under 35 U.S.C. §112, first paragraph, because the specification, while being enabling for a human SDF-5 protein having a molecular weight of about 30 to 35 kd comprising the amino acid sequence of SEQ ID NO:3, does not reasonably provide enablement for the ability to regulate the transcription of one or more genes. In order to advance prosecution, Applicants have cancelled claim 25 without consideration of the merits of the rejections and reserve the right to pursue the subject matter of claim 25 in one or more continuing or divisional applications.

The Examiner has indicated that if Applicants are able to overcome the pending rejections under 35 USC §112 first paragraph, claims 19, 20, 23, 25, and 29 would still be rejected under 35 U.S.C. §112, first paragraph, because the specification, while being enabling for a human SDF-5 protein comprising SEQ ID NO:2, does not reasonably provide enablement for a truncated human SDF-5 protein as recited in SEQ ID NO:3 or the claims as written.

Claim 20 has been amended to depend from claim 18 and claim 25 has been deleted. As stated in the specification (page 5, line 27-35), the truncated sequence set forth in SEQ ID NO:3 is based in part on the Von Heginje signal peptide prediction algorithm whereby the first 17-24 amino acids appear to be involved in signaling for the secretion of the mature peptide. It is expected, therefore, that the active species SDF-5 exists as a heterogeneous population of active species with varying N-termini.

Applicants submit, therefore, that the specification provides support for the claimed truncated human SDF-5 proteins. It is clear to one skilled in the art that the active protein may not include the amino acids comprising the signal peptide sequence. One skilled in the art would recognize that truncation of the signal peptide sequence, which

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function lies in the secretion of the mature peptide, would not diminish the activity of the mature protein, and it is within the knowledge of one skilled in the art to assay for such activity without undue experimentation.

In view of the foregoing amendments and remarks, Applicants respectfully request reconsideration and reexamination of this application and timely allowance of the pending claims. Should the Examiner believe that a telephonic interview would assist in clarifying any remaining issues, or to otherwise expedite prosecution, Applicants respectfully invite the Examiner to call the undersigned attorney at (617) 452-1661.

Please grant any extensions of time required to enter this response and charge any additional required fees to our deposit account 06-0916.

Respectfully submitted,

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Dated: August 26, 2002

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Claim Amendments With Markings to Show Changes Made

Claim 20 has been amended as follows:

Claim 20. A composition for the formation and/or maintenance of chondrocyte and/or cartilaginous tissue in a patient in need of same comprising a therapeutic amount of the human SDF-5 protein according to claim ~~19~~ 18 in a pharmaceutical carrier.

Claim 25 has been deleted.

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APPENDIX A

18. A purified human SDF-5 polypeptide comprising the amino acid sequence of SEQ ID NO:2 or SEQ ID NO:3.

19. A purified human SDF-5 protein produced by the steps of
(a) culturing a cell transformed with a DNA molecule comprising the nucleotide sequence from nucleotide #316 to #1143 as shown in SEQ ID NO: 1; and
(b) recovering and purifying from said culture medium a protein comprising the amino acid sequence from amino acid #21 to amino acid #295 as shown in SEQ ID NO:2.

20. A composition for the formation and/or maintenance of chondrocyte and/or cartilaginous tissue in a patient in need of same comprising a therapeutic amount of the human SDF-5 protein according to claim 18 in a pharmaceutical carrier.

22. A purified human SDF-5 protein comprising the amino acid sequence from amino acid #1 to #295 of SEQ ID NO:2.

23. A purified human SDF-5 protein comprising the amino acid sequence from amino acid #1 to #275 of SEQ ID NO:3.

29. A purified human SDF-5 polypeptide comprising an amino acid sequence selected from the group consisting of:
(a) Amino acids 1, 18, 19, 20, 21, 22, 23, 24 or 25 to 295 of SEQ ID NO:2; and
(b) amino acids 1 to 275 of SEQ ID NO:3.

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Procedure: 6675

Cell Biology, Women's Health Research Institute
Peter V. N. Bodine, Ph.D., Helga Ponce-de-Leon, B.S.

April 15, 2002

TITLE: A cell based secondary assay for in vitro measurement of SFRP antagonist activity in human osteoblasts

SHORT TITLE: HOB SFRP TCF-Luciferase assay

PROJECT NO.: 1141

PURPOSE: Secreted frizzled related protein-1 (SFRP-1) is a Wnt antagonist and is expressed in osteoblasts and osteocytes. Deletion of SFRP-1 in mice leads to decreased osteoblast/osteocyte apoptosis and increased bone formation. This cell-based assay will be used to determine the selectivity of inhibitors for SFRP-1 versus other SFRP family members. It will also be used to determine the species specificity of these inhibitors towards human, mouse and rat SFRP-1. These compounds may be novel anabolic bone agents for the treatment of osteoporosis.

**MATERIALS AND
METHODS:**

Cells

HOB-03-CE6 cells, a conditionally immortalized human osteoblast cell line, are grown in T-175 flasks in growth medium: phenol-red free DMEM/F12 (GIBCO/BRL) with 10% heat inactivated FBS (Fetal Bovine Serum), 1% GlutaMAX-1, 1% PenStrep and 1% MEM Sodium Pyruvate. The cells are passaged twice weekly (Mondays, Fridays). The seeding density is 3.0×10^6 cells / flask. The cells double every 2 to 3 days at 34°C in a 5% CO₂, 95% air humidified incubator and confluence should not exceed 85%.

One day prior to transfection, the cells are plated with growth medium

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into one of the following formats: 150,000 cells/well in 1ml medium into 24 well plates; 55,000 cells/well in 0.5 ml medium into 48 well plates; 22,000 cells/well in 0.2 ml medium into 96 well plates. Routinely, the cells are plated about 12 PM, then incubated at 34°C overnight.

Routine Co-Transfection

The growth medium is removed, the cells are re-fed with one of the following: 0.5 of growth medium in 24 well plates, 0.2 ml of growth medium in 48 plates, 0.1 ml of growth medium in 96-well plates.

24 well plates:

For each well of cells to be transfected, the following DNAs are diluted together in 50 ul OPTI-MEM 1 (Gibco/BRL, reduced serum medium, Cat# 31985-070): 16xTCF Luciferase Reporter (634-1) **1120 ng**, hTCF-1 **35 ng**, hWnt-1, hWnt-3 or hWnt-3a **70 ng** (or empty vector pUSEamp, all from Upstate Biotechnology), hSFRP-1, -2, -3, -4, or -5, mSFRP-1, rSFRP-1 **280 ng**, CMV b-Gal (Clontech) **20 ng**; a total of **1525 ng** cDNA/well.

48 well plates:

For each well of cells to be transfected, the following DNAs are diluted together in 25 ul OPTI-MEM 1 (Gibco/BRL, reduced serum medium, Cat# 31985-070): 16xTCF Luciferase Reporter (634-1) **386 ng**, hTCF-1 **12.1 ng**, hWnt-1, hWnt-3 or Wnt-3a **24 ng** (or empty vector), hSFRP-1, -2, -3, -4, or -5, mSFRP-1, rSFRP-1 **97 ng**, CMV b-Gal **6.9 ng**; a total of **526 ng** cDNA/well.

96 well plates:

For each well of cells to be transfected, the following DNAs are diluted together in 25 ul OPTI-MEM 1 (Gibco/BRL, reduced serum medium, Cat# 31985-070): 16xTCF Luciferase Reporter (634-1) **167.2 ng**, hTCF-1 **5.2 ng**, hWnt-1, hWnt-3 or Wnt-3a **10.4 ng** (or empty vector), hSFRP-1, -2, -3, -4, or -5, mSFRP-1, rSFRP-1 **41.8 ng**, CMV b-Gal **3.0 ng**; a total of **228 ng** cDNA/well.

For each well of cells to be transfected in **24 well plates**, 1ul of Liptofectamine 2000 (Invitrogen) is diluted in 50 ul OPTI-MEM 1 medium and incubated at room temperature for 5 minutes. The diluted DNAs are then combined with the diluted Liptofectamine 2000 [LF2000]. This mixture is incubated at room temperature for 20 minutes. Fifty micro-liter of the DNA-LF2000 mixture is added to each well. The plates are incubated at 34°C in a 5% CO₂/95% humidified air incubator for 4 hours.

For each well of cells to be transfected in **48 well plates**, 0.34 ul of LF2000 is diluted in 25 ul OPTI-MEM 1 medium and incubated at room temperature for 5 minutes. The diluted DNAs are then combined with the diluted LF2000. This mixture is incubated at room temperature for 20 minutes. Fifty micro-liter of the

DNA-LF2000 mixture is added to each well. The plates are incubated at 34°C in a 5% CO₂/95% humidified air incubator for 4 hours.

For each well of cells to be transfected in **96 well plates**, 0.16 ul of LF2000 is diluted in 25 ul OPTI-MEM 1 medium and incubated at room temperature for 5 minutes. The diluted DNAs are then combined with the diluted LF2000. This mixture is incubated at room temperature for 20 minutes. Fifty micro-liter of the DNA-LF2000 mixture is added to each well. The plates are incubated at 34°C in a 5% CO₂/95% humidified air incubator for 4 hours.

Following the 4-hour transfection the cells are washed once with growth medium, re-fed with 1 ml (24-well plate), or with 0.5 ml (48-well plate), or with 0.2 ml (96-well plate) of the same. The plates are then incubated overnight at 34°C.

The next morning, the medium is changed to fresh growth medium (same volume as before) with treatment containing either vehicle (typically 0.1% DMSO) or diluted compounds in replicates of 4-wells/compound in 24-well plates, 6-wells/compound in 48-well plates, or 8-wells/compound in 96-well plates. The cells are then incubated at 37°C for 24 hours.

Assay

After treatment, the cells are washed once with Hanks' Balanced Salt Solution w/o calcium, magnesium, phenol red and lysed with 50ul/well of 1x cell culture lysis reagent (Promega, Cat# E153A) on a shaker at room temperature for 25 minutes. Thirty micro-liter aliquots of the cell lysates are transferred to 96-well luminometer plates (from DYNEX Technologies, Inc.; Microlite 2+ flat bottom microtiter plates, Part # 7572). Luciferase activity is measured in a MicroLumat LB96P (EG&Berthold) or in a Victor (PE) Luminometer using 100ul/well of luciferase substrate (Cat# E151A). Following the injection of substrate, luciferase activity is measured for 10 seconds after a 1 second delay. Similarly, 10 ul aliquots of the cell lysates are transferred to separate 96-well luminometer plates for β -Gal activity and 70ul of Galacton chemiluminescent substrate (Tropix, # ABL120R) is added to each well. The plates are covered (kept dark) and incubated at room temperature for 1 hour. β -Gal activity is measured in a MicroLumat LB96P (EG&Berthold) or Victor (PE) luminometer using 100ul/well of Light Emission Accelerator (Tropix, # ABX210A). Following the injection of the accelerant, β -Gal activity is measured for 5 seconds after a 3 seconds delay. The luciferase and β -Gal activity data are transferred from the luminometer to a PC Excel program and analyzed using the SAS/Excel program. After the luciferase activity is normalized to β -Gal, the SAS/Excel program is used to determine the mean and standard deviation of each treatment and to analyze the data for statistical significance and to determine EC50 values.

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ANALYSIS OF RESULTS:

The luciferase data is analyzed using the SAS/Excel program. For the initial single dose experiment, if the compound treatment results in significantly increased reporter activity as determined by a T-test versus the SFRP control, then the results are reported as fold induction over the SFRP control. Compounds passing this initial test will then be evaluated for EC50 determinations using dose response curves typically five log doses per curve.

REFERENCE COMPOUNDS:

WAY-205227 is a known inhibitor of GSK-3, a key enzyme involved in Wnt signaling pathway. The inhibition of GSK-3 results in stabilization of β -catenin, leading to up-regulation LEF/TCF regulated reporter genes. The compound serves as an internal control for measurement of cellular response to Wnt signaling.

RADIS FIELDS:

Compound:	W- AR compound designation Batch No Salt
Procedure Number:	6675
Project Number:	1141
Experiment Completion Date:	DD/MO/YR experiment completed
Investigator/Title:	Last Name, First Name/Title
Notebook Number:	Notebook number where the experiment is recorded
Concentration:	Compound concentration in assay (default = 10^{-6} M)
Fold induction with hSFRP-1:	Compound/hSFRP-1 control
Fold induction with hSFRP-2:	Compound/hSFRP-2 control
Fold induction with hSFRP-3:	Compound/hSFRP-3 control

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Fold induction with hSFRP-4:	Compound/hSFRP-4 control
Fold induction with hSFRP-5:	Compound/hSFRP-5 control
Fold induction with mSFRP-1:	Compound/mSFRP-1 control
Fold induction with rSFRP-1:	Compound/rSFRP-1 control
Species specific	Yes / No
Selective SFRP-1 inhibitor	Yes / No
EC50 in uM	Compound concentration required to inhibit 50% SFRP action
EC50 for hSFRP-1	
EC50 for hSFRP-2	
EC50 for hSFRP-3	
EC50 for hSFRP-4	
EC50 for hSFRP-5	
EC50 for mSFRP-1	
EC50 for rSFRP-1	
Comments:	

CLASSIFICATION

KEYWORDS: SFRP-1, SFRP-2, SFRP-3, SFRP-4, SFRP-5, Wnt, and Osteoporosis

Is this a primary, secondary, tertiary etc. procedure. Secondary assay

Is this procedure a High-throughput screen or a manual screen?

Manual screen

Body System/Cell line/Tissue type: HOB-03-CE6 Human Osteoblast

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cell line

Mechanistic Target: SFRP-1 antagonist

Therapeutic Target: Osteoporosis

in vivo or *in vitro*? In vitro

REFERENCES:

Finch, P.W., He,X., Kelly,M.J., Uren, A., Schaudies, R.P., Popescu, N.C., Rudikoff, S., Aaronson S.A., Varmas, H.E., Rubin, J.S. Purification and molecular cloning of a secreted, Frizzled –related antagonist of Wnt action. 1997 Proc. Natl. Acad. Sci. U.S.A. 94, 6770-6775

Coghlan, M.P., Culbert, A.A., Cross, D.AE., Corcoran, S.L., Yates, J.W., Pearce, N.J., Rausch, O.L., Murphy, G.J., Carter, P.S., Cox, L.R., Mills, D., Brown, M.J., Haigh, D., Ward, R.W., Smith, D.G., Murray, K.J., Reith, A.D., Holder, J.C. Selective small molecule inhibitors of glycogen synthase kinase-3 modulate glycogen metabolism and gene transcription. 2000, Chemistry and Biology, 7, 793-803

Peter V.N. Bodine, Jack Green, Heather A. Harris, Ramesh A. Bhat, Gary S. Stein, Jane B. Lian, and Barry S. Komm. Functional properties of a conditional phenotype, Estrogen-responsive Human Osteoblast Cell Line. 1997 Journal of Cellular Biochemistry 65:368-387

Peter V.N. Bodine, Patent No: WO200119855-A2, Assignee: American Home Product Corporation. Madison, N.J., USA. Composition comprising a secreted frizzled related protein – useful for the treatment of e.g. osteoarthritis.

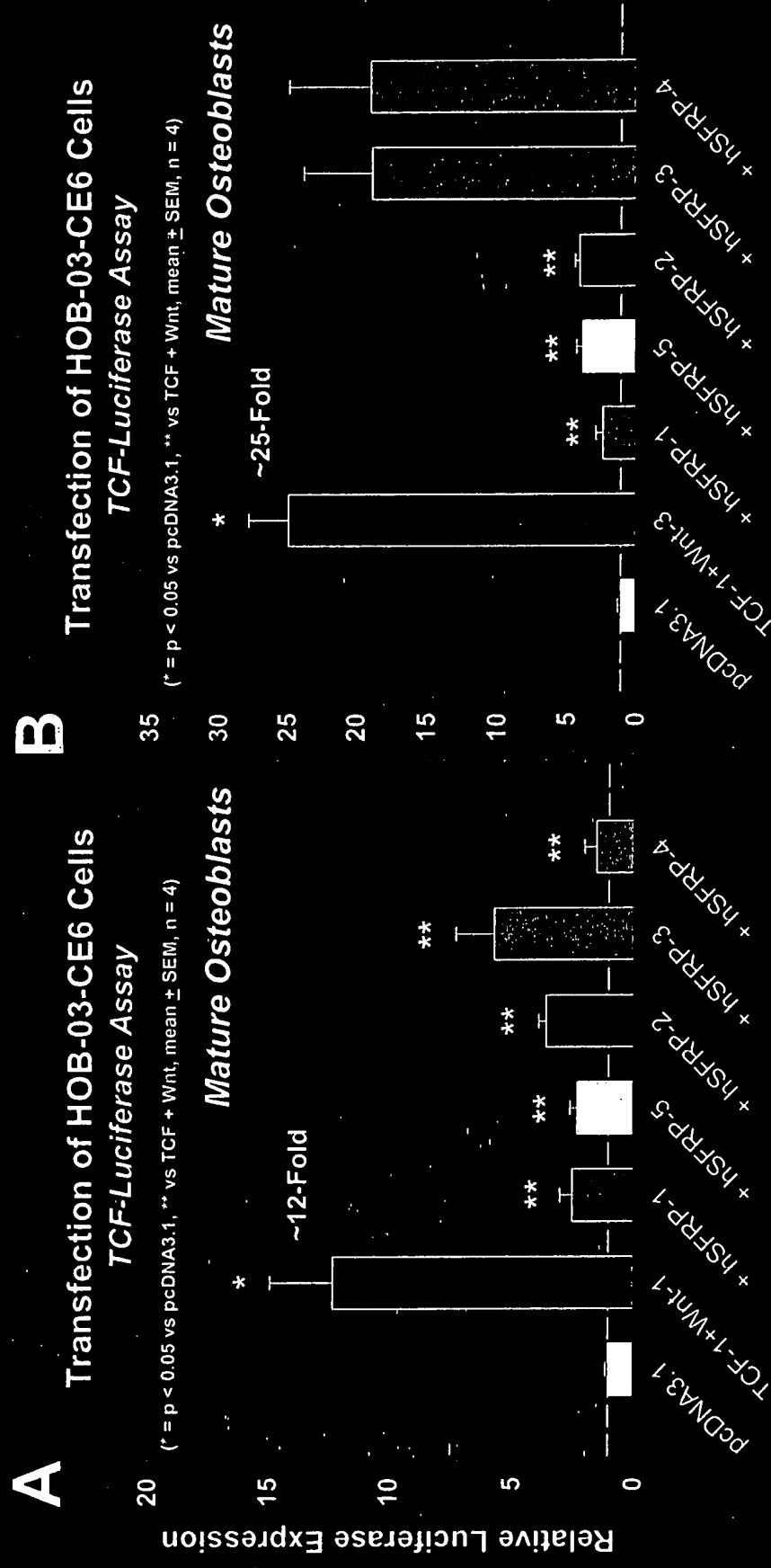
Cornelia Leimeister, Alexandra Bach, Manfred Gessler. Developmental expression patterns of mouse sFRP genes encoding members of the secreted frizzled related protein family. 1998 Mechanisms of Development 75, 20-42

2ndary Assay for SFRP-1 Antagonists

HOB SFRP TCF-Luciferase Assay: RADIS # 6675

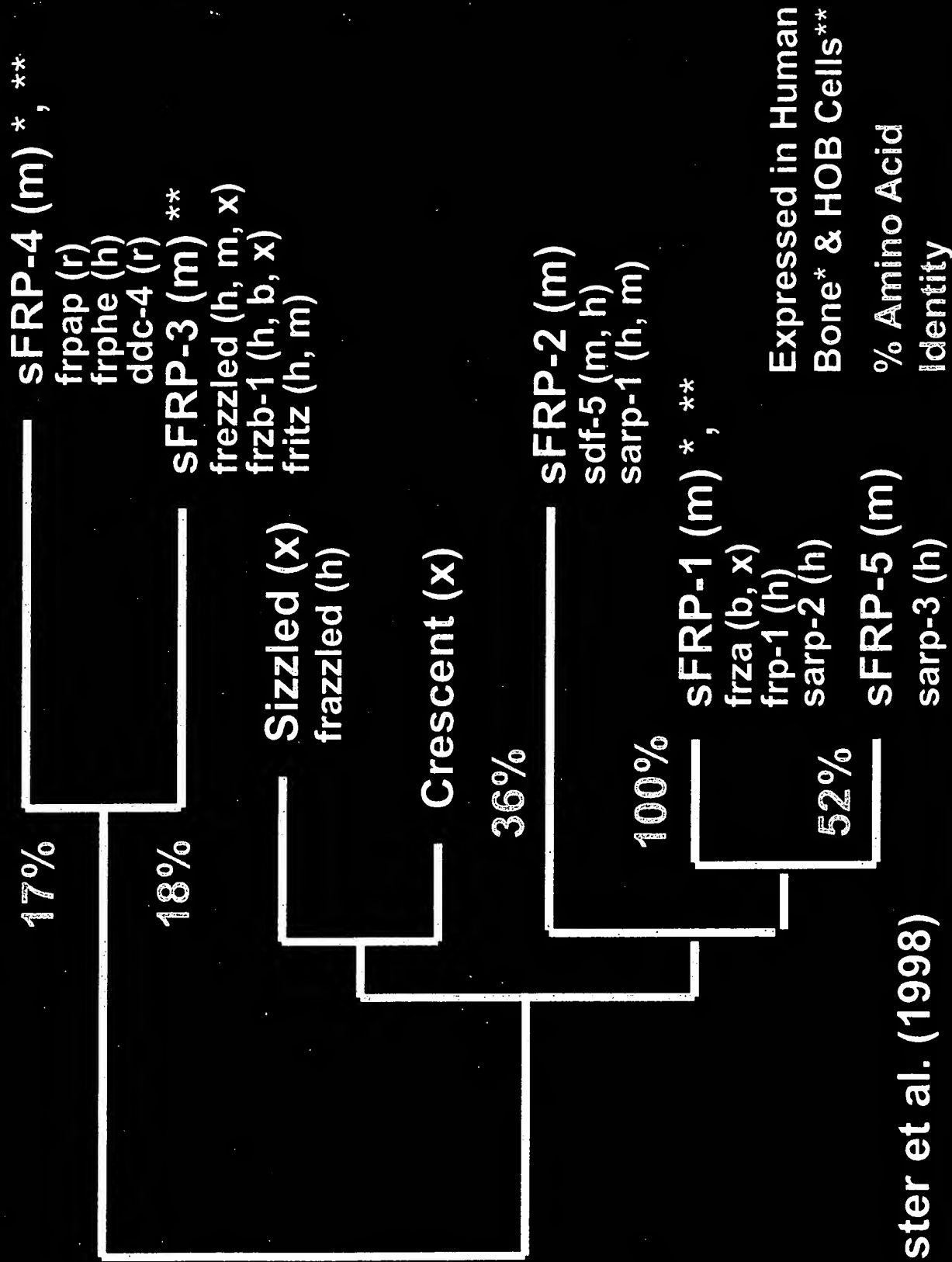
Wnt-1

Wnt-3



This Assay Measures Specificity for SFRP Family Members as well as Species Specificity for Human, Mouse and Rat

sFRP Phylogenetic Tree



Expressed in Human Bone* & HOB Cells**

% Amino Acid Identity

Leimeister et al. (1998)